PATENT
Docket No. 204372000300

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Margaret P. Drosos

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Lynn E. Spitler et al.

Serial No.: 08/105,444

Filing Date: August 11, 1993

For: PROSTATIC CANCER VACCINE

Examiner: P. Gambel

Group Art Unit: ~~1806~~ 1806

APPEAL BRIEF TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Transmitted herewith, in triplicate, is an Appeal Brief for the above-identified application.

☒ A verified Statement(s) of Small Entity Status was previously submitted.

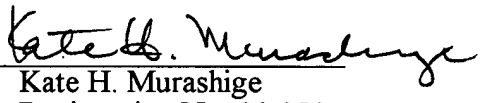
☒ Petition for Extension of Time is enclosed.

☒ Attached is the Appeal Brief fee of $145.00.

☐ Please charge the Appeal Fee of $145.00 to **Deposit Account No. 03-1952.**

The Assistant Commissioner is hereby authorized to charge any fees under 37 C.F.R. § 1.17 which may be required by this paper, or to credit any overpayment, to **Deposit Account No. 03-1952.** A duplicate copy of this sheet is enclosed.

Dated: December 7, 1995

By: 

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PATENT
Docket No. 204372000300

12/29/96

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For: PROSTATIC CANCER VACCINE

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APPLICANT'S BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Appellants hereby appeal from the final rejection of claims 1-40 mailed 7 March 1995. A Notice of Appeal was filed along with a Petition for an Extension of Time on 7 August 1995. A Petition for an Extension of Time for filing the Brief of two months to extend the time for response to 7 December 1995 is attached hereto along with the required fee. Appellants respectfully request that the rejections be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee.

dc-16485

I. Real Party in Interest

The present application is assigned to Jenner Technologies, a California corporation.

II. Related Appeals and Interferences

Appellants are aware of no interferences and no other appeals which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. Status of claims

The application was filed with claims 1-40. All of these claims, some of them in amended form, remain pending and are rejected. The rejection of all of claims 1-40 is appealed.

IV. Status of Amendments

In response to a final rejection herein, appellants submitted an amendment to claim 21. According to Advisory Actions mailed 15 August 1995 and 8 September 1995, this amendment was to be entered upon filing an appeal.

V. Summary of the Invention

Prior art formulations for vaccines designed to produce an antitumor response from an immune system have been based on the use of antigens that are uniquely associated with the tumors *per se*. The present invention represents a different approach in that rather than such uniquely tumor-associated antigens as active ingredients, the present invention employs antigens that are associated with the host prostate tissue -- that is, they are found in the prostate in contrast to other tissues. Generally, they are found both in the normal prostate and in malignant prostate tissue. (See page 4, lines 8-19.)

The antigen which is associated with prostate-specifically, whether normal or malignant, can be supplied in a variety of ways. First, it can be supplied formulated as the antigen *per se* in a suitable vaccine formulation. Second, if a protein or peptide, the vaccine may contain an expression system which is able to produce the protein or peptide *in situ* in the subject. Third, an antiidiotypic antibody which mimics the antigen may be used in its place (see page 5, lines 1-9). The invention is directed both to the vaccines and to their methods of use. (See page 4, lines 20-30.)

Thus, claims 1-7 are directed to methods of vaccinating subjects either bearing prostate tumors or at risk for acquiring prostate tumors using the vaccines of the invention. Claims 8-14 are directed to vaccines for this purpose where the antigen is supplied in the form of an expression system for its generation *in situ*. Claims 15-20, similarly are directed to vaccines wherein the antigen is supplied in the form of an antiidiotypic antibody that mimics the antigen. Claim 21 is directed to a form of the vaccine where the antigen is present *per se* and wherein it is encapsulated in or coupled to a liposome. Claims 22-27 are directed to forms of the vaccine wherein the antigen can be in any one of the possible forms, but wherein there are at least two active ingredients included in the vaccine. Claims 28-33 are directed to forms of the vaccine wherein the active ingredient comprises at least one immunologically effective portion of the antigen. Claims 34-40 are directed to forms of the vaccine wherein the antigen is in its native form, but wherein it is other than human prostate-specific antigen (PSA) produced in human cells. The reason for so many subsets of claims to vaccines is to avoid any incidental anticipation by the Chu *et al.* patent discussed below, describing simply purification of PSA from human prostate tissue and the use of this antigen to raise antibodies for diagnostic purposes.

A more thorough discussion of the particular types of active ingredients represented in these sets of claims can be found on page 6 beginning at line 4 through page 7, line 11. Antigens which are already known to be associated with the prostate gland are described on page 7, line 13 through page 10, line 2. The methods and vaccines of the invention, however, apply equally to any antigen subsequently found to characterize prostate tissue.

VI. Issues

The following issues are presented for review.

1. Whether it is mandatory to include *in vivo* clinical data in order to support claims to methods of inducing an antitumor immune response and to compositions for this purpose, as set forth in the rejection of the claims under 35 U.S.C. § 112, first paragraph.

2. Whether the vaccines and methods of the present invention must be limited to those derived from antigens associated with the prostate gland whose existence is already established, or whether, having established the principle of using the host's prostate tissue as the source of antigens for vaccination, appellants are entitled to claims that embrace additional antigens subsequently shown to be associated with prostate tissue in high levels. This is reflected in an additional rejection under 35 U.S.C. § 112, first paragraph on the basis of asserted overbreadth.

3. Whether the claims may properly include immunologically effective portions of the antigens or the antiidiotypic antibodies mimicking them as active ingredients within the rubric of the claims. This is also reflected in a rejection made under 35 U.S.C. § 112, first paragraph.

4. Whether the claimed methods and vaccines are obvious under 35 U.S.C. § 103 over the combination of Chu *et al.* (U.S. Patent No. 4,446,122) in view of Dai *et al.* (*FASEB J* (1988) **2**:A2301; Deguchi *et al. Cancer Research* (1986) **46**:3751-3755; Brown *et al.* (U.S. Patent No. 5,262,177); and Alving *J Immunol Meth* (1991) **140**:1-13.

VII. Grouping of Claims

Although the applicability of the various references cited under 35 U.S.C. § 103 varies with the particular subject matter of the claims (for example, the Alving reference is applicable only to claim 21 among the independent claims) the inventive concept of all claims is the same and all claims may be considered together for purposes of the rejection under 35 U.S.C. § 103.

However, it should be evident that the rejection under 35 U.S.C. § 112, as set forth in issue No. 2 above, is inapplicable to claims 3, 9, 16, 23, 29, and 36 since these claims are already limited to the three specific known antigens: prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), and prostatic acid phosphatase (PAP). Issue No. 2 relates to whether the antigens used as the basis for the vaccine can be other than these specifically named antigens.

VIII. Argument

It is believed that issues 1-4 should be resolved in favor of appellants for the following reasons:

A. The Federal Circuit has clearly and repeatedly held that *in vivo* clinical data are unnecessary to support claims to pharmacological utilities.

Appellants rely on the holding and dicta in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995) and the cases cited therein in support of their position that is unnecessary to supply *in vivo* clinical data in support of claims of the type proposed here. The Examiner is certainly correct that the compounds asserted to have pharmacological activity in *Brana* are small molecules as opposed to antigens which, for the most part, are proteins and that the Brana compounds were structurally similar to other compounds known in the art that had been successful in animal models. The Examiner is not correct that in *Brana*, "animal models were art recognized to be predictive of therapeutic usefulness." Indeed, the court objected that the references cited by the Office in *Brana* "merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility."

This statement of the court should be carefully considered. It clearly implies that it is unnecessary that appellants must prove the ultimate value in humans of their asserted utility. If the "implication" needs to be stated more directly, the court does so at 1442 where it says

> The (Office) confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption.

Later on the same page, the court states

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The Federal Circuit could not have been clearer that the kinds of potential problems which the Examiner speculates might occur are not relevant to the issue of 101/112 enablement. The court clearly recognized that there are many steps between disclosing basic pharmacological utility and overcoming the kinds of common problems that may intervene and require further research before a medicament or vaccine can be administered to humans. This is perfectly consistent with meeting the requirements under 35 U.S.C. § 112, first paragraph. This has been consistently the position of the Federal Circuit as pointed out by the court in its citation of *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985) and several other cases mentioned in Note 11 on page 1439.

Of course, the availability of additional or better data in the *Brana* case as compared to any data available here is irrelevant in the face of the clearly enunciated principles as set down by the court. An additional principle noted by *Brana* is that a rejection, essentially based on doubts that the invention will work as described, is the same rejection whether it is framed under 35 U.S.C. § 101 or 35 U.S.C. § 112. Appellants note here that the rejection under 35 U.S.C. § 101 has been withdrawn; it would appear appropriate to withdraw the rejection under 35 U.S.C. § 112, to the extent that it is based on doubts as to efficacy, just as was the rejection under § 101.

It should be noted that there is no assertion in the record that the application fails to describe how to make and use the invention, nor is there an assertion that the best mode is not

disclosed. The sole basis for this aspect of the rejection under § 112 is a simple doubt that the invention will work as is fully described.

The Examiner appears also to misunderstand the allocation of burden of proof. The final rejection at page 4 states, "In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicants' arguments have not been found persuasive." This is certainly a misstatement of the law. The appellants are not obliged to provide "clear and convincing evidence" that the invention will perform as described. On the contrary, it is the burden of the Office to set forth a *prima facie* case for doubting the description made by the appellants. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

To the extent that the Examiner here has raised doubts based on "scientific reasoning" they either relate to the kinds of clinical problem areas that routinely intervene between a basic pharmaceutical invention and actual clinical application (e.g., "the protein may be inactivated before producing an effect," "the protein may not reach the target area," "other functional properties... may make the protein unsuitable for *in vivo* therapeutic use"; etc.) or reside in the assertion that other workers have not succeeded in formulating a vaccine that has been approved by the FDA for treatment of any form of cancer. This latter is an extremely peculiar kind of reasoning under any circumstances. The fact that the art has failed to solve a problem that the invention purports to solve is hardly a basis for concluding that the invention does not solve it either.

The publication cited by the Office (Ezzell, *J NIH Research* (1995) 7:46-49) is putatively a review of cancer vaccines in general. The criticisms quoted by the Examiner are that "tumor cells *in vivo* simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes." [Emphasis added.] Presumably for this reason, there is no optimism that such proteins can be used successfully in vaccines. This has nothing to do with the invention because the invention does not employ antigens that are "unique" to tumors. The invention is based on use of an antigen that is overrepresented in the host tissue. The Examiner is correct that the antigens may also be expressed on benign or malignant tumor cells, but the fact that they are also displayed on normal prostate cells makes them not "unique to the tumor." They therefore do

not necessarily suffer from the defects proposed by Ezzell as characteristic of such "unique" tumor antigens. Since the Ezzell comments are directed only to these antigens, they are irrelevant with respect to the invention claimed here.

In summary, with respect to Issue No. 1, it is respectfully submitted 1) that the Examiner is in error in asserting that appellants are obliged to provide "clear and convincing evidence" of efficacy; 2) that the Examiner has failed to adduce a *prima facie* case that the statements made by appellants in their specification are unbelievable, and 3) that the Federal Circuit has clearly held that clinical problems of the type about which the Examiner speculates are not relevant to a consideration of patentable utility. To the extent that the rejection under 35 U.S.C. § 112, resides in an asserted lack of utility, as set forth in Issue No. 1 set forth above, this basis for rejection should be withdrawn.

B. Appellants should not be limited to only those antigens that are currently known in the art to be associated with the prostate.

The invention resides in the recognition that a host tissue antigen, which antigen is shared with a tumor inhabiting the host tissue, and which antigen distinguishes immunologically the tissue from other types of normal tissue in the host can be used to elicit an immune response against prostate tumor. It happens that three such antigens are already known: PSA, PSMA, and PAP. Appellants do not claim to have identified or discovered these antigens or to have purified them to homogeneity, or manipulated them in any way other than to have described them as active ingredients in a vaccine. As appellants pointed out in their supplementary response to the final rejection, citing Wright, G.L. *et al.*, *Int J Cancer* (1991) **47**:717-725 and Beckett, M.L. *et al.*, *Cancer Res* (1991) **51**:1326-1333, additional antigens have been described in the art which are distinguishable from PSA, PSMA and PAP.

As set forth in the submission of these abstracts, these disclosures simply point out that there is no reason to believe that all antigens which are characteristic of the prostate have to date been described. Since appellants' invention does not relate to the discovery and description of these antigens, but rather to a method to use them once they are discovered, it would appear

unfair to limit the claims to those prostate-specific antigens that happen to be known at the time the present inventors' application was written or which had come to their attention at that time.

The situation is analogous to claims drafted to expression systems for production of various proteins. Perhaps there is a particularly strong or a particularly well regulated promoter than can be used generally for the production of recombinant proteins. It would not make sense to limit claims to an expression system involving this promoter only to genes that are known at the time that the use of the promoter in recombinant expression was invented. The nature of the genes is irrelevant to the invention as claimed.

Similarly, here, the repertoire of known prostate-characteristic antigens is not a part of the invention; rather it is the method of using this repertoire that is at issue.

Two additional notes: first, once again, the Examiner applies an inappropriate standard by requiring "clear and convincing evidence commensurate in scope with the allegations and claims." This is an impermissible shifting of the burden of proof. *In re Marzocchi (supra)*. Second, this rejection for asserted overbreadth under 35 U.S.C. § 112, first paragraph, is inapplicable to claims limited to PSA, PSMA and PAP -- i.e., claims 3, 9, 16, 23, 29, and 36.

Because appellants' invention relates to a method to use members of the repertoire of prostate-characteristic antigens, it is improper to limit appellants only to those antigens whose existence happens to coincide in time with the appellants' invention. Reversal of this basis for rejection is therefore requested.

C. "Immunologically effective portions" of antigens and antibodies are properly included in the claims.

It appears from the Advisory Action mailed 15 August 1995 that only the 35 U.S.C. § 112, first paragraph rejection as directed to the inclusion in the claims of "immunologically effective portions" is maintained. In the bridging sentence in the two-page attachment to the Advisory Action, the Examiner states, "While the Examiner acknowledges that the various fragment forms claimed can elicit an immune response, applicants' invention..." and no further comment is made. Therefore, this argument focuses on this particular aspect. It is assumed that

objections to the terms "at least one antigen overrepresented in the prostate gland," "peptide," and "exhibits posttranslational modifications different from those of PSA produced in human cells" mentioned in connection with a 35 U.S.C. § 112, first and second paragraph rejections in the final Office action have been dropped.

Appellants are unable to find any rationale provided by the Examiner to explain why "immunologically effective portions" should not be included. Indeed, appellants gratefully note the Examiner himself acknowledges, as quoted above, that various fragment forms can elicit an immune response. Indeed, this is well known; it is well understood currently in the art that an antigen represents a collection of epitopes, and that individual epitopes or combinations of epitopes can be used to elicit an immune response. It is also well understood that for antiidiotypic antibodies, only the variable regions are responsible for the mimicry of the underlying antigen. There is just no basis provided by the Examiner for excluding immunologically effective portions of the claimed antigen or antiidiotypic antibody that goes beyond the rationale for the § 112 rejection as applied to the complete antigen or antibody. The errors of the rejection as to the complete antigen or antibody have already been argued in paragraph A of this section, and these arguments are incorporated here. The Examiner again cites Ezzell in support of his position that the vaccines and methods of the invention generally will not work. As pointed out above, leaving aside any legal arguments with regard to burden of proof, Ezzell concerns vaccines that are prepared from antigens that are unique to tumor tissue as opposed to normal tissue; the invention methods and vaccines are designed to overcome any problems associated with them.

Since the Examiner has adduced no reasons, other than those adduced with respect to complete antigen that "immunologically effective portions" of antigens and antibodies would be ineffective, it is believed proper to include such portions within the scope of the present claims.

D. The prior art references cited, taking individually or together, fail to suggest the present invention.

The basis for this rejection appears to reside in the general involvement of antigens characteristic of the prostate in treatment of prostate cancer. The rejection fails to recognize how different the claimed approach is from that taught by the references. The difference can be

succinctly stated once again: An antigen shared by the normal cells of the prostate with prostate tumors (not unique to the tumor) is used to elicit an active immune response against the tumor (not as a target for an immunoconjugate). Appellants are unable to find any suggestion in this combination of references that a normal tissue antigen shared by the tumor should be used to elicit an active tumor response. The Examiner has been unable to point to any such suggestion.

Appellants certainly recognize that it is the combination of references that has been applied not the references individually; however, it will be helpful initially to summarize the teachings of each reference.

Chu is directed to isolation and purification of a particular prostate-characteristic antigen apparently not previously recognized, termed prostate-specific antigen (PSA) (or PA in the Chu reference). The antigen is purified from either normal or cancerous human prostate tissue. The human PSA is disclosed as capable of raising antibodies in animals which antibodies then can be used in immunotherapy and diagnosis. The Examiner points to column 6, paragraph 1 as showing the use of PSA in "immunospecific chemotherapy" and to column 7, paragraph 3 as showing its use in "vaccine preparation." What do these paragraphs actually say?

Column 6, paragraph 1 is mostly concerned with the use of antibodies prepared in animals for diagnosis of prostate cancer in humans by assessing the level of PSA in serum. At the end of the paragraph is a sentence which reads, "Immune-specific chemotherapy also is a potential area where much work can now be initiated with the availability of PA immunologic reagents e.g. C.T. Ghose in *J Nat Cancer Inst* **61**:657 (1978)."

Appellants submitted an abstract of the Ghose article with their response to the final rejection, the complete article is enclosed with this brief. The abstract and article confirm that, indeed, this sentence refers to immunoconjugates involving antibodies against a target antigen prepared outside the human host to be treated (i.e., in animals) coupled to some kind of toxin or chemotherapeutic agent. The immunoconjugate is then putatively directed to the target tissue by virtue of the immunospecificity of the antigen. This is an entirely different approach from using the target antigen as a <u>vaccine in the host itself</u> to elicit an antitumor immune response.

Turning to column 7, paragraph 3, the first sentence states that "Conventional vaccine preparation techniques can be used." But for what? "For the preparation of immunogens suitable for preparing diagnostic antibodies against the human prostate antigen." This is not a "vaccine" for eliciting an antitumor response in a subject against its own tumor. This is a vaccine simply for raising antibodies against an antigen for subsequent use *ex vivo* to the immunized host. The mice, rats or rabbits used to prepare these antibodies surely were not selected because they were at risk for prostate tumors or because the contain prostate tumors. These are irrelevant hosts used only as antibody generating factories. The raising of antibodies in these hosts is certainly not a method to induce an antitumor immune response in a potential or actual prostate tumor-bearing subject, as required by claim 1. This is an antibody manufacturing procedure.

It might be regarded as curious that despite the recognition that PSA can, like any other protein, be used to elicit antibodies immunoreactive with it, there is no suggestion whatsoever in Chu that whatever immune response is elicited would be directed to a prostate tumor in a subject to which the "vaccine" is administered. The only suggestion in Chu that relates to the use of PSA in any kind of therapeutic protocol teaches away from the approach of the present invention -- rather it suggests the production of antibodies in an irrelevant host which can then be used simply as targeting agents to carry a toxin or chemotherapeutic agent to a tumor marker.

Appellants recognize that vaccine compositions containing human PSA isolated from human tissue would be coincidentally anticipated by Chu even though their use in the method of the invention is not described or suggested (but rather taught away from) by Chu. Therefore, claims directed to the vaccines *per se* do not include claims to PSA isolated from human tissue. Rather, claims 8-14 are directed to vaccines containing recombinant expression systems for the tumor-characteristic antigens; claims 15-20 contain claims to vaccines wherein the antigen is an antiidiotypic antibody; claim 21 specifically requires liposomes as an excipient; claims 22-27 require at least two active ingredients that represent tumor-characteristic antigens; claims 28-33 require that only an immunologically effective portion of the antigen be present; and claims 34-40 contain a proviso that the antigen be other than human prostate-specific antigen in a form produced in human cells. These vaccines are clearly not suggested by the Chu reference which

describes only isolated human PSA as a means for generating, in irrelevant hosts, antibodies useful in diagnostics or in immunoconjugates.

The next reference cited is Dai *et al.* which is directed to monoclonal antiidiotypic antibodies that mimic rat prostate tumor. In order to obtain these antiids, rats were immunized with a "murine monoclonal antitumor antibody (Ab1) that recognized a membrane antigen of Dunning rat prostate tumor." The antigen is specifically designated "rat tumor membrane antigen (RTMA)" and is thus a tumor-unique antigen, conventional in approaches to cancer antitumor vaccines. Dai, thus, teaches away from the present invention which envisions using an antigen shared by normal prostate and prostate tumor. The Dai reference merely confirms that antigens can be mimicked by antiidiotypic antibodies which could be substituted for such antigens in the anticancer vaccines of the prior art employing unique tumor antigens. Thus, while Dai teaches "the value of antiidiotypic antibodies to modulate the immune response to prostate tumor" (whatever modulate here means) the teaching is solely in the context of conventional unique tumor antigens.

Deguchi describes the same conventional chemotherapeutic methods using immunoconjugates as were described by Chu for PSA. Using another prostate-characteristic antigen as the target (PAP) Deguchi teaches "targeting PAP as a therapeutic modality." However, this is totally different from the approach used by the invention where PAP or its representative is used to elicit an active immune response in the host himself. This conventional therapeutic method teaches away from the approach of the present invention in the same manner as does Chu.

Brown *et al.* is cited simply for its teachings that conventional prior art antitumor vaccine antigens, which are unique to the tumor targeted, can be formulated as recombinant expression systems contained in viruses. Similar to Dai, this reference shows that there are alternative forms in which unique tumor antigens can be presented in vaccines other than as the antigens themselves.

Finally, the paper by Alving describes liposomes as carriers of antigens and adjuvants. Alving is relevant only to those claims which require liposomes as excipients. The only independent claim with this requirement is claim 21; this requirement is also in claims 17-18 dependent on claim 15; claims 24-25 dependent on claim 22; claims 30-31 dependent on claim 29; and claims 37-38 dependent on claim 34. The use of liposomes is as excipients is not relied upon for patentability; as explained above it appears in independent claim 21 merely to avoid an inherent and accidental anticipation by the Chu reference with respect to vaccine containing isolated human PSA.

Taken in total, then, what do these references teach? First, they teach that antigens unique to tumor tissue can be used as active ingredients in antitumor vaccines in order to elicit antitumor responses in a host to which they are administered and that these antigens can either be supplied *per se* or in the forms of antiidiotypic antibodies or in the forms of expression systems for production of the antigens *in situ*. This is acknowledged prior art. The entire focus of the prior art in terms of eliciting an immune response to tumor tissue has been to supply antigens which are unique to the tumors *per se*. There is no suggestion in any of this literature to use antigens characteristic of the host tissue.

But, according to the Examiner, antigens shared by the tumor and the host tissue have been used as targets for immunoconjugates in chemotherapeutic protocols, citing Chu and Deguchi. Appellants assume that the argument must then be (although it is never precisely stated in the rejection) that if the shared antigens can be used as chemotherapeutic immunoconjugate targets, and if unique tumor antigens are used in antitumor vaccines, there is no reason that the shared antigens could not also be used as active ingredients in antitumor vaccines.

The problem with this argument is that only appellants have thought to do this. The Examiner, using the invention as a guide, has extracted only those aspects of the teachings of Deguchi and Chu that are relevant to the invention and combined them after the fact with only those teachings of Dai and Brown that are relevant to the present invention. It is precisely this kind of hindsight rejection that the Federal Circuit has repeatedly held to be unsupportable. *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540; 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983);

Orthopedic Equipment Co. v. United States, 702 F.2d 1005; 217 U.S.P.Q. 193 (Fed. Cir. 1983); and *In re Sernaker*, 702 F.2d 989; 217 U.S.P.Q. 1 (Fed. Cir. 1983).

What possibly could motivate a reader of Chu or of Deguchi, which describe making immunoconjugates directed to PSA or PAP to look to the Dai and Brown publications except the guidance of the invention itself? There is nothing in Chu or Deguchi which relates to an active immune response against tumors; there is nothing in Dai or Brown that relates to immunoconjugate-mediated chemotherapy. These are two separate prior art approaches that have independently developed. Absent the teachings of the invention, there is no reason to combine these teachings.

And even after having combined them, using the invention as a guide, having read them all, would it have been obvious to the ordinarily skilled practitioner that the target for the immunoconjugate should be used as an antigen for an active antitumor vaccine? No. It does not follow that a substance which guides a toxic agent to the proximity of the tumor would elicit an active immune response to the tumor, especially in view of its presence in normal tissue.

The position of the Examiner apparently is that there is no distinction between the use of antigens which are unique to tumors and those that are shared by the tumor and the prostate tissue host. Appellants do not understand this argument. Appellants also believe that the Examiner has improperly shifted the burden of proof by stating that appellants have not "provided any evidence that the antigen targeted by Dai *et al.* is not expressed by prostate tissue." Dai *et al.* on its face relates to an antigen uniquely produced by tumor membranes.

For the reasons stated above, appellants believe that the combination of references cited in support of the rejection under 35 U.S.C. § 103 could have been made only using the invention as a guide and that even the combination of these references does not render the present invention obvious.

IX. Appendix

Attached hereto is an appendix containing a copy of the claims involved in the Appeal.

Conclusion

For the reasons stated above, appellants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph for asserted lack of efficacy and asserted overbreadth as well as that over the art be reversed and claims 1-40 passed to issue.

The Assistant Commissioner is hereby authorized to charge any fees under 37 C.F.R. § 1.17 which may be required by this paper, or to credit any overpayment, to **Deposit Account No. 03-1952.** A duplicate copy of this sheet is enclosed.

Dated: December 6, 1995.

Respectfully submitted,

By: Kate H. Murashige

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